REMARKS

I. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. Enablement Rejection

Claims 1-11, 14, 17, 24, 27 and 30-45 were rejected under 35 U.S.C. § 112, first paragraph, because, allegedly, the specification, while enabling for methods of producing heterologous polypeptides or peptides or proteins in *Lactococcus lactis* does not reasonably provide enablement for methods of producing heterologous polypeptides, peptides or proteins in any lactic acid bacteria. It was additionally alleged that the specification does not enable "...any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims". Office Action, page 2. Several factors, discussed below, based on *In re Wands*[1], were relied upon as the basis for this rejection.

The nature of the invention was characterized as a method of producing heterologous proteins in lactic acid bacteria, using chemically defined media and fed-batch or continuous cultivation. Office Action, page 3.

Applicants generally agree with this summary of the invention, but wish to point out that the claimed methods are also directed to the production of heterologous peptides and polypetides.

It was admitted in the Office Action that the state of the prior art was advanced, since methods of cell culture for the production of heterologous proteins were well known, although (it was asserted) the field was well developed for use of such well

[1] In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

known hosts as *E. coli*, but not for non-traditional recombinant hosts, such as lactic acid bacteria. *Id.*

Applicants agree that the state of the prior art was advanced, but do not necessarily agree that the field was not well developed for recombinant lactic acid bacteria as hosts. Applicants respectfully point out that at least during the decade preceding the filing date of the application (i.e., in the very early 1990's) increasing focus was placed in the art on the development of lactic acid bacteria (LAB) for the production of homologous or heterologous peptides, polypeptides and proteins. *See*, e.g. Applicants' specification, page 2, line 16 - page 3, line 20.

The relative skill of those in the art was asserted to be moderate, insofar that, generally, trial and error was used to determine optimal conditions for obtaining maximal amounts of a recombinant protein during cell culture. *Id.*

It was also stated that the

> "... level of predictability of the art is very high, since it cannot be accurately predicted which growth media and conditions will result in maximal amounts of a recombinant protein in any particular cell type. For example, Jensen et al. (Appl. Environ. Micriobiol. 59, 12, p. 4363-4366, 1993) disclosed that one particular lactic acid bacteria, Lactococcus lactis, has numerous growth requirements which required a particular combination of amino acids for sufficient growth, and that experimentation was required to determine appropriate conditions (page 4363). There is no expectation that the particular growth conditions needed for L. lactis would be appropriate for other types of lactic acid bacterial.

Id.

Applicants respectfully traverse these assertions.

The use of chemically defined media for cultivating a wide range of lactobacilli and *Pediocuccus* has been known in the art for some time. For example, *see* Imbert et al., On the Iron Requirement of Lactobacilli Grown In Chemically Defined Medium, Curr Microbiol., 1998 Jul; 37(1):64-6, describing studies of the iron requirements of four strains of lactobacilli in a synthetic medium under aerobic or anaerobic conditions. Also *see* Elli et al., Iron Requirement Of Lactobacillus spp. in Completely Chemically Defined

Growth Media, J Appl Microbiol, 2000 Apr; 88(4):695-703, reporting on the development of a completely chemically-defined growth medium for *Lactobacillus johnsonii*, based on statistically-designed techniques suitable for other lactobaccilli.

Similarly, Petry et al., Factors Affecting Exocellular Polysaccharide Production by Lactobacillus delbrueckii subsp. bulgaricus Grown in a Chemically Defined Medium., Appl Environ Microbiol. 2000 Aug; 66(8): 3427-31, describe a chemically defined medium containing lactose or glucose as the carbon source, which supports growth and exopolysaccharide production of two strains of *Lactobacillus delbrueckii* subsp. *bulgaricus*.

Glaasker et al., Osmotic Regulation of Intracellular Solute Pools in Lactobacillus plantarum, J Bacteriol. 1996 Feb; 178(3):575-82 report that the cytoplasmic pools of K+, proline, glutamate, alanine, and glycine of *Lactobacillus plantarum* ATCC 14917 increased when the osmolarity of the growth media was raised from 0.20 to 1.51 osmol/lkg by KCl. They also state that when glycine-betaine was present in a high-osmolarity chemically defined medium, it was accumulated to a high cytoplasmic concentration, but the concentrations of most other osmotically important solutes decreased.

Zygmunt WA; Reversal of d-Cycloserine Inhibition of Bacterial Growth by Alanine, J Bacteriol. 1962 Jul; 84(1):154-6, describe the comparison of the reversal of the anti-bacterial activity of d-4-amino-3-isoxazolidone by alanine in bacterial cultures actively growing on chemically defined media in cultures requiring exogenous alanine and those capable of its synthesis. They state that dl-Alanine was the most effective reversal agent in *Pediococcus cerevisiae*, an alanine-requiring organism.

These publications establish a relatively high level of skill in the art and predictability of results obtained with chemically defined media among different bacterial species, and extend beyond the largest groups of lactic acid bacteria used in the industry, i.e., *Lactococcus spp.* and *Lactobacillus spp.*

Another basis for the alleged failure to meet the enablement requirement for the claims by the Applicants' specification was the limited number of working examples, all using *Lactococcus lactis*. It was also suggested that the claims have a large breadth since they are drawn to methods:

> ...using any lactic acid bacteria, and therefore encompass[es] all types of bacteria which includes such diverse organisms as defined in the specification, as follows: 'Lactococcus spp., Streptococcus spp., Lactobacillus spp., Leuconostoc spp., Pediococcus spp., Brevibacterium spp., Propionibacterium spp. Additionally, lactic acid producing bacteria belonging to the group 30 of the strictly anaerobic bacteria, bifidobacteria, i.e. Bifidobacterium spp., which are frequently used as food starter cultures alone or in combination with lactic acid bacteria, are generally included in the group of lactic acid bacteria' (page 6 of the specification).

Office Action, page 4.

While Applicants agree that their working examples are directed to methods using *Lactococcus lactis*, it is well established that working examples are not necessary, at least to satisfy the written description requirement, e.g., see *Falkner et al. v. Inglis et al.* 448 F.3d 1357, 1365, 79 USPQ2d 1001 (CAFC 2006).

Furthermore, just because Applicants' claims are not limited to any particular lactic acid bacterial species, it does not mean they are not enabled by the specification. For example, in *Falkner*, the Federal Circuit reviewed the decision of the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences ("Board"), in the case where one of the issues was enablement of a claim directed to a vaccine comprising, in pertinent part, an effective immunizing amount of a mutant poxvirus and which has a genome with an inactivating mutation in a viral gene, the viral gene being essential for the production of an infectious new virus particles, the mutant poxvirus being able to cause production of infectious new virus particles in a complementing host cell gene, but unable to cause production of infectious new virus particles when the mutant poxvirus infects a host cell. Falkner alleged that the aforementioned claim (of Inglis), failed to meet the enablement requirement because Inglis' specification focused on a

subgenus of herpes virus (instead of the poxvirus) and because the specification contained a detailed example of an embodiment comprising herpes virus but not a poxvirus. The Board held that Inglis' specification provided enablement for the full scope of his claims and stated:

> ...because the differences between the herpes viruses and poxviruses were well known, this would have aided a person with ordinary skill in the art in her application of the lessons of the herpes virus example in the construction of poxvirus vaccines. The mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this art. Indeed, great expenditures of time and effort were ordinary in the field of vaccine preparation. *Id.*

The Federal Circuit affirmed.

Similarly, Applicants provided in their specification an extensive disclosure of the types of bacteria that can be used in their invention, including the anaerobic bacteria *Bifidobacterium spp*. Persons of ordinary skill in the art would readily understand the similarities and differences between the *Lactococcus lactis* and any other LAB, including B*ifidobacterium spp*., which would inform them how to adapt detailed teachings based on *Lactococcus lactis* to any other LAB covered by Applicants' claims.

It was also asserted in the Office Action that the specification provides limited amount of guidance because "...the only guidance in the specification is limited to the disclosed method as applied to Lactococcus lactis." Office Action, page 4.

Again, Applicants respectfully disagree with this assertion. The specification (as correctly observed in the Office Action, e.g., at page 4), is not limited to *Lactococcus lactis*, but instead includes a description of a number of lactic acid bacteria. *See*, for example, page 6, lines 24-30. Reiterating arguments set forth above, persons of ordinary skill in the art, familiar with Applicants' specification, including detailed examples, would readily understand how to make and use Applicants' claimed methods with the bacteria encompassed by their claims.

B. Written Description Rejection

Claims 6 and 35 were rejected under 35 U.S.C. § 112, first paragraph, allegedly for failure to comply with the written description requirement. The rejection was premised on the assertion that the specification does not define what is encompassed by the term "derivative" (in the context of the claim language "the regulatable promoter is the P170 promoter disclosed in WO 98/10079 or a derivative thereof") and that claims 6 and 35 are genus claims in terms of a nucleotide sequence which functions as a regulatable promoter of an undefined structure or sequence. The disclosure was further criticized for not being descriptive of the complete structure of a representative number of species encompassed by the claims, since, allegedly, one skilled in the art cannot envision all DNA molecules which have regulatable promoter activity in the lactic acid bacteria and are derived from the P170 promoter. It was also asserted that there was no disclosure in the specification of the precise nucleotides in the P170 promoter which could be modified by insertion, substitution or deletion and yet retain regulatable promoter activity in lactic acid bacteria. It was concluded that the specification does not describe the claimed DNA in such full, clear, concise and exact terms to indicate that Applicants had possession of the product when the application was filed. Office Action, page 5.

Applicants respectfully traverse this assertion.

Applicants submit that the assertion that a derivative of the P170 regulatable promoter can be any nucleotide sequence which is a regulatable promoter derived from another substitution, addition or deletion, is not compatible with the dictionary meaning of the word "derivative", nor with the knowledge in and state of the art. According to Webster's Encyclopedic Unabridged Dictionary of the English Language, Gramercy; revised edition, 1989, a "derivative" is "a substance or compound obtained from, or regarded as derived from, another substance or compound". *See* page 389. As pointed out in *Falkner et al. v. Inglis et al.*, "[w]ritten description is a question of fact, judged from the perspective of one of ordinary skill in the art as of the relevant filing date." 448 F.3d 1357, 1363. It is known in the art that a first nucleotide sequence

having no structural resemblance to a second nucleotide sequence would not be "obtained from" or be "regarded as derived from" the second sequence. Persons skilled in the art will understand that a DNA sequence which is a derivative of another sequence has structural resemblance to that other sequence, and that such derivatives are frequently referred to as equivalent nucleotide sequences. Such persons would be capable of preparing a derivative of a known sequence and would know how to ensure that the derivative would have properties required for its utilization in Applicants' claimed methods.

For example, it is known in the art to optimize the codon usage when transferring a DNA sequence from one species to another. This process does not change the function of the DNA sequence, but merely improves the function of such sequence.

C. 35 U.S.C. §112, Second Paragraph, Rejection

Claims 5 and 34 were rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite because the term "derived" (in the context of the claimed language "the regulatable promoter is derived from a lactic acid bacterium") is nonspecific and relative in nature for which Applicants provided no definition. Office Action, page 6.

Applicants respectfully traverse this rejection. In their specification, Applicants described the promoter and derivation thereof from various sources, known in the art, for example, see page 8 lines 22-32. The P170 promoter or a derivative thereof is taught in the specification to be pH inducible, where the P170 promoter is induced by low pH. See page 3 lines 10-20; page 4 lines 31-33; and page 8, line 22 – page 9, line 19. The productivity and kinetics of the P170 expression system is taught in the specification, e.g., in Example 3 and utilization thereof in Examples 4-7. Therefore, the metes and bounds of the limitation are clearly delineated in the specification, as will be apparent to one of ordinary skill in the art , based on his or her knowledge, aided by the specification. Thus, claims 5 and 34 are definite.

II. CONCLUSION

Applicants respectfully submit that the application is in condition for allowance and respectfully request a notice of allowance for the pending claims. Should the Examiner determine that any further action is necessary to place this application in condition for allowance, the Examiner is kindly requested and encouraged to telephone Applicants' undersigned representative to resolve any issues in an expeditious manner and place the application in condition for allowance.

It is believed that no additional fee is due in connection with this filing. However, in the event that any fees are necessary, the Commissioner is hereby authorized to charge our Deposit Account No. 50-2478.

Respectfully submitted,

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